REMARKS

Status of the Claims

Claims 1-4, 6-10, 12, 16, 23, 28-29 and 33-43 are pending in the application. By this paper, claims 1, 23 and 29 are amended. No new matter has been added.

In light of the amendments and remarks presented herein, Applicants respectfully request reconsideration and allowance of claims 1-4, 6-10, 12, 16, 23, 28-29 and 33-43.

Request for Withdrawal of Final Rejection

Applicants object to the purported "finality" of the Office Action dated March 30, 2010 on the grounds that the Examiner has raised a substantially new ground for rejection in asserting that the combination of Badylak et al., U.S. Patent Application Pub. No. 2003/0216811, Badylak et al. (Biomaterials 1999) and Penn et al., U.S. Patent Application Pub. No. 2004/01611412 render claims 1-4, 6, 12, 23, 25, 26, 28, 40, 41 and 43 obvious.

The Badylak references, both newly cited, were purportedly applied by the Examiner because of their disclosure of "*submuscosa tissue-derived grafts and methods of using said grafts to repair damaged or diseased tissue.*" There is no basis for the Examiner's assertion on page 24 of the Office Action that "Applicant's amendment *necessitated* the new ground(s) for rejection."

The January 4, 2010 amendments essentially revised principal claims 1 and 23 to remove the step of *encapsulating* transfected cells prior to seeding such cells onto a matrix. (The removed cell encapsulation step was reintroduced in claims 10 and 33.) In the latest Office Action, the Examiner is apparently arguing that a sheet of small intestinal submucosa (SIS) is the same as the polymeric matrix (or matrix material) of Applicant's claims. Nothing in Applicant's amendment changed the scope of the recited matrix element in any of the claims. Since the scope of the claimed *matrix element* was not changed at all, the citation of the Badylak references (as disclosures of matrix materials) is a new ground for rejection under MPEP 706.07(a) precluding the issuance of a final rejection.

Restriction of Claims 7, 38-39 and 42

Reconsideration of the newly-raised restriction requirement and examination of claims 7, 38, 39 and 42 on their merits is also respectfully requested. There is no basis for the Examiner's assertion that "the species of vascular endothelial cells and myoblasts have been *constructively elected* by original presentation for prosecution on the merits." In fact, the original claims (filed in 2004) including claim 5, which recited "co-adminstering a second population of cells" – without restriction to vascular endothelial cells or myoblasts. Moreover, claim 6 (which was the subject of four prior Office Actions) further defined the second population of cells to comprise "*undifferentiated cells.*" Both of these claims encompass endothelial progenitor cells – and neither claim was the subject of a restriction requirement during the six-year pendency of this application. Hence, the Examiner's assertion of *constructive election* by the applicant is plainly incorrect.

Additionally, claim 7 originally recited that the second population comprises *vascular endothelial cells*. The amendment to which the Examiner objects would simply *narrow* this claim to *endothelial progenitor cells*. Applicant's specification clearly defines vascular endothelial cells as *including* endothelial progenitor cells. See, for example, paragraph [0120]:

> In another aspect of the present invention, tissue neovascularization can be enhanced using transient expression of VEGF and ***vascular endothelial cells (EC)*** within the tissue that incorporate into blood capillaries. ***Various types of EC including***, but not limited to, . . . ***progenitor EC*** . . . ***can be used*** for angiogenesis and vasculogenesis.

(Emphasis added.) See also, paragraph [0124]. Thus, the amendment to claim 7 does not switch species at all but rather simply narrows the claim. The same reasoning also applies to new claims 38-39 and 42. Accordingly, the restriction requirement should be withdrawn for this reason, as well, and claims 7, 38-39 and 42 should be examined on their merits.

Amendment to the Claims

Claim 29 has been amended to correct antecedent basis. No new matter has been added.

The Invention

The current invention is directed to a method of organ augmentation by co-administration of two populations of cells with different functions. A *first population of cells* is *transiently transfected* to express an *angiogenesis modulating agent*, and a *second population of cells to be assimilated* at the target site.

Independent claim 1 is directed to a method of organ augmentation using the two populations of cultured cells, *the first population transiently transfected to express VEGF* and *the second population to assimulate* at the target region, implanted together in an *injectable polymer matrix* to induce assimilation and differentiation at the target region.

Independent claim 23 is directed to a method that involves implanting a *first population of cultured cells transiently transfected with a plasmid expressing an angiogenesis modulating agent* with a *second population of cultured cells* in an *organ construct* such that the angiogenesis modulating agent induces the second population of cells to *assimilate and differentiate* at the target site.

Nowhere in the references cited by the Examiner, either alone or in combination, is there a teaching or suggestion of the claimed invention.

Rejection under 35 U.S.C. 11, second paragraph

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for lacking antecedent basis.

The Examiner is thanked for noting the lack of antecedent basis for the term " the *encapsulated* population of cells" in claim 29. The above amendments correct this indefiniteness by deletion of the word "*encapsulated*" from claim 29.

Rejection under 35 U.S.C. 103(a)

Claims 1-4, 6, 8-9, 12, 23, 25-26, 28, 40-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Badylak et al. (US 2003/0216811), in light of Badylak et al. (Biomaterials, 1999) and in view of Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants respectfully disagree.

The Office Action cites Badylak (2003) for teaching the use of endothelial cells in a submucosa tissue graft. The Office Action further cites Badylak (1999) as teaching injectable intestinal submucosa and Penn for teaching skeletal myoblasts transfected with VEGF.

Applicants agree with the Office Action that Badylak (2003) discloses a "tissue graft comprising a vertebrate intestinal submuscosa tissue seeded with endothelial cells and at least one additional cell population." According to Badylak(2003), the additional cell population "can be a population of non-keratinized or keratinized *epithelial* cells or a population of *mesodermally derived* cells selected from the group consisting of fibroblasts, smooth muscle cells, skeletal muscle cells, cardiac muscle cells, multi-potential progenitor cells, pericytes, osteogenic cells, and any other suitable cell type, preferably selected based on the tissue to be repaired."

In short, Badylak (2003) provides nothing but vague instructions for what else can be added to his composition in addition to *endothelial* cells: (1) *epithelial* cells – cells arranged in one or more layers that form part of a covering or lining of a body surface; and (2) *mesodermal* cells – tissue derived from the middle germ layer of the embryo, e.g., muscle and bone and cartilage, blood or connective tissue. By reciting *endothelial, mesodermal and epithelial* cells, Badylak (2003) essentially covers almost <u>all</u> possible naturally occurring cell types.

Badylak (2003) does not enable one skilled in the art to carry out the invention without undue experimentation. To select Applicants' additional cell population (*cultured cells transiently transfected to express an angiogenesis modulating agent*) from the universe of cells suggested by Badylak (<u>all</u> mesodermal and epithelial cell types) is an epitome of undue experimentation.

Moreover, Badylak (2003) provides no examples whatsoever of his "*at least one additional cell population.*" The only experimental results involve endothelial cells alone seeded on a submucosa sheet.

Not only are there no working examples provided of the "additional cell population," Badylak (2003) clearly does not appreciate the utility of an additional population that is *transiently transfected to express an angiogenesis modulating agent*, or *VEGF*, in particular.

The addition of Badylak (1999) does not remedy the deficiencies of Badylak (2003). Nowhere in Badylak (1999) is there any suggestion regarding the use of two populations of *cultured* cells with different functions, much less a first population of cultured cells that *transiently express an angiogenesis modulating agent* and a second population of cultured cells that will *assimilate and differentiate* at the target site.

Badylak (1999) is a study comparing *hydrated and dehydrated sheets* of intestinal submucosa as cell culturing media. (See Fig. 1 of Badylak (1999) illustrating the dehydrated and hydrated sheets of material). Badylak (1999) concludes that endothelial cells adhere better to hydrated sheets. The only discussions of angiogenesis modulating agents in Badylak are found on page 2257 where the authors note that submucosa is naturally rich in factors such as VEGF and on page 2262 where the authors state it is "possible" that such growth factors may play a role in cell *adherence* to the submucosa sheets.

Furthermore, the combination of Badylak (2003) and Badylak (1999) with Penn also does not render the claims 1 and 23 obvious as Penn merely teaches transfecting myoblasts with VEGF to *induce VEGF expression in ischemic tissue.* The Office Action asserts that "one skilled in the would have found it obvious to utilize the transiently transfected myoblasts of Penn et al. as the 'at least one additional exogenous cell population' in the graft of Badylak et al...."

The Office Action fails to provide any "nexus" between the primary and secondary references. Badylak (2003) offers nothing more than vague suggestions (e.g., "*any other suitable cell type*") as to where one skilled in the art could look for the "at least one additional exogeneous cell population." The combination of Badylak with Penn is simply hindsight reconstruction of the Applicants' invention. The Examiner is relying on the present invention as

an instruction manual or "template" to piece together various disclosures from the prior art to arrive at the claimed invention.

None of the references, alone or in combination, teach or suggest Applicants' methods of organ augmentation utilizing *an injectable polymer matrix* with a *first population of cultured cells* that will *express the VEGF angiogenesis modulating agent* and a *second population of cultured cells to be assimilated* at a target tissue region, as in claim 1, or utilizing a *first population of cultured cells express the angiogenesis modulating agent* and a *second population of cultured cells on a matrix material* that assimilate and differentiate at the target site, as in claim 23.

Therefore, claims 1-4, 6, 8-9, 12, 23, 25-26, 28, 40-41 and 43 are non-obvious and patentable over Badylak (2003), Badylak (1999) and Penn. Applicants respectfully request reconsideration.

Claims 1-4, 6, 8-10, 12, 23, 25-26, 28, 33-37, 40-41 and 43 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Badylak et al. (US 2003/0216811), in light of Badylak et al. (Biomaterials, 1999) and in view of Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065) and Stewart et al. (US 2006/0251630 A1). Applicants again respectfully disagree.

This ground for rejection appears to be an unnecessary duplication of the Examiner's first ground for rejection except with regard to claims 10 and 33-37 (which recite the additional step of *encapsulating the transfected first population of cells*). The Examiner cites Stewart as teaching encapsulation. However, Stewart does not remedy the deficiencies of Badylak (2003), Badylak (1999) and Penn.

Applicant's arguments for non-obviousness over Badylak (2003), Badylak (1999) and Penn are described above. For the sake of brevity, they are not repeated but instead incorporated by reference.

Stewart is directed to encapsulating cells for transplantation to protect against the recipient's immune system response. However, nowhere in Stewart is there any teachings or suggestions that would remedy the deficiencies of Badylak (2003), Badylak (1999) and Penn.

Nor does the combination of the references teach or suggest the invention of claims 10 and 33-37. In fact, it appears that the Examiner is simply picking and choosing features from various pieces of art and combining them to arrive at the claimed invention.

The Office Action fails to provide any "nexus" between the primary, secondary and tertiary references. The combination of Stewart with Badylak (2003), Badylak (1999) and Penn is simply hindsight reconstruction of the Applicants' invention.

In order to satisfy the burden of obviousness in light of combination, it is not enough to pick and choose features from various pieces of art and just combine them to arrive at the claimed invention without any support for making such combinations. (*In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed. Cir. 1988).) As explained in *KSR International Co. v. Teleflex, Inc.*, "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there *must be some articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness." (MPEP § 2142, citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); emphasis added; *see also* MPEP § 2143.01.) Furthermore, the Board must guard against impermissible hindsight obtained from the knowledge of the invention of the present application and the Examiner may not "use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." (*In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (citation omitted).)

None of Badylak (2003), Badylak (1999) and Penn teaches or suggests a need to encapsulate cells or identify a problem that encapsulation would solve. Again, no reason has been articulated to combine Steward with Badylak (2003), Badylak (1999) and Penn. Simply asserting that Steward shows that any cell can be encapsulated to prevent immune rejection does not provide any nexus or a valid reason to combine the references. To rely on Steward, itself, as the reason to combine is pure hindsight reconstruction.

As there is no valid reason to combine the references other than the Applicants invention, claims 1-4, 6, 8-10, 12, 23, 25-26, 28, 33-37, 40-41 and 43 are non-obvious and patentable over Badylak (2003), Badylak (1999), Penn and Steward.

Claims 23, 25-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants again respectfully disagree.

The Office Action cites Naughton as teaching a method for promoting blood vessel formation in tissues and organs with a three-dimensional stromal tissue construct. However, Naughton fails to teach coadministration of two separate populations of cells with different functions, i.e., *a transiently transfected first population of cultured cells expressing an angiogenesis modulating agent* and a *second population of cells that assimilate and differentiate at the target site.*

The March 30, 2010 Office Action states on page 4 that the stromal cells are being considered the second cell population and Naughton clearly intends for the stromal cells to assimilate into the existing tissue. However, Naughton intends for both the fibroblasts and any other stromal cells to be seeded *onto* the three-dimensional framework, see paragraph [0039] of Naughton. Moreover, Naughton has no appreciation for the use of *two different populations* of cultured cells, such as *a transiently transfected first population* of cells implanted with *an organ construct* (a second population of cultured cells seeded on a matrix).

In fact, Naughton discusses the other stromal cells as an *alternative* to the fibroblasts for seeding onto the three-dimensional framework to support long term growth. See, for example, paragraph [0039]:

> For example, other cells found in loose connective tissue may be inoculated onto the three-dimensional framework along with, or instead of, fibroblasts. Such cells include but are not limited to endothelial cells, pericytes, macrophages, monocytes, adipocytes, skeletal muscle cells, smooth muscle cells, cardiac muscle cells, etc. Such cells may be inoculated onto the three-dimensional framework ***in the absence of fibroblasts***. (Emphasis added.)

Clearly, Naughton teaches away from the use of two populations of cells and actually intends for one population of cells, to be inoculated onto the three-dimensional framework. The Examiner notes that paragraphs 0046-0050 describe genetic engineering techniques for augmenting the functions of the implanted stromal cells. However, again, there is no teaching or suggestion that

a *separate* cell population of transfected cells can be used to induce the assimilation and differentiation of implanted cells, much less the advantages of a transiently transfected population that expresses an angiogenesis factor for a limited period of time.

The Office action further cites Penn as teaching a method for transiently transfecting a population of skeletal myoblasts with VEGF. However, Penn does not remedy the deficiencies of Naughton. Penn is directed to transfection of skeletal myoblasts with VEGF and has no appreciation for multiple populations of cultured cells where one population is transiently transfected to express an angiogenesis agent and another population is seeded onto a matrix to assimilate and differentiate at a target site.

The Office Action fails to provide any "nexus" between the primary and secondary references. Naughton discloses implantable constructs of stromal tissue to promote tissue repair and regeneration. Naughton offers nothing more than vague suggestions for augmenting the functions of the stromal cells. The combination of Naughton with Penn is simply hindsight reconstruction of the Applicants' invention. The Examiner is relying on the present invention as an instruction manual or "template" to piece together disclosures from the prior art to arrive at the claimed invention.

Again, in order to satisfy the burden of obviousness in light of a combination of references, it is not enough to pick and choose features from various pieces of art and just combine them to arrive at the claimed invention without any support for making such combinations. (*In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed. Cir. 1988).) As explained in *KSR International Co. v. Teleflex, Inc.*, "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there *must be some articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness." (MPEP § 2142, citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); emphasis added; *see also* MPEP § 2143.01.) The Examiner may not "use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." (*In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (citation omitted).)

Since neither reference, alone or in combination, teaches or suggests the method of claim 23, much less the methods recited in the claims that depend therefrom, the claimed invention cannot be rendered obvious. Again, Applicants respectfully request reconsideration.

Claims 23, 25, 26, 28, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants again respectfully disagree.

This rejection is essentially a reiteration of the previous 103 rejection with the addition of claims 40 and 41. The arguments presented above are the same for claims 40-41. Neither of the cited references teaches or suggests a method of augmenting organ function with two separate populations of cultured cells providing different functions, a *first population of cells* that *expresses an angiogenesis modulating agent* and a *second population of cells seeded onto a matrix* that *assimilates and differentiates* at the target site.

Furthermore, the Office Action states it would have been obvious to one of ordinary skill in the art to utilize the vascular endothelial cells within the organ construct of Naughton and employ the myoblasts of Penn. However, the reasoning in the Office Action again amounts to mere hindsight reconstruction. In fact, it appears that the Office Action is simply picking and choosing features from various pieces of art and combining them to arrive at the claimed invention without providing a valid reason why one of ordinary skill in the art would combine the elements in exactly the same way.

As there is no valid reason to combine the references other than the Applicants invention, and Naughton actually teaches away from the use of more than one population of cells, claims 23, 25, 26, 28, 40 and 41 are non-obvious and patentable over the cited references. Therefore, Applicants respectfully request reconsideration and allowance of claims 23, 25, 26, 28, 40 and 41.

Claims 23-26 and 28 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Penn et al. (US 2004/0161412 A1,

60/405,274 and 60/424,065) and Atala et al. (US Patent 6,479,064). Applicants respectfully disagree.

The reasons for non-obviousness over Naughton and Penn are detailed above and incorporated by reference. The Office Action further cites Atala et al. to remedy the deficiencies of Naughton and Penn. Specifically, the Office action cites Atala as teaching decellularized tissues as the three-dimensional matrix.

The addition of Atala to Naughton and Penn still does not render the claimed invention obvious. None of the references have any appreciation for the use of *two different populations* of cultured cells, a *first population of cells* that *expresses an angiogenesis modulating agent* and a *second population of cells seeded onto a matrix* that *assimilates and differentiates* at the target site.

As stated above, the only apparent reasoning for combining Naughton with the Penn and Atala references is hindsight reconstruction. No reason has been given why one of ordinary skill in the art would combine Naughton's tissue constructs with Penn's transfected cells or Atala's decellularized matrices. The Examiner is once more relying on the present invention as an instruction manual or "template" to piece together various disclosures from the prior art to arrive at the claimed invention.

As the additional references fail to remedy the deficiencies of Naughton and do not amount to a teaching or suggestion of the claimed invention, the invention of claims 23-26 and 28 is non-obvious and patentable. Therefore, Applicants respectfully request withdrawal of the obviousness rejection and reconsideration of claims 23-26 and 28.

Claims 23, 25-26, 28, 33 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065) and Stewart et al. (US 2006/0251630 A1). Applicants again respectfully disagree.

Naughton, Penn and Stewart are all described above. The arguments against obviousness in light of these references are again incorporated by reference. The Examiner's obviousness

argument combines Naughton as teaching a tissue construct to improve cardiac function, Penn as teaching transient transfection of VEGF in myoblasts and Stewart as encapsulating cells to protect transplanted cells against immune system responses.

Once more, the Office Action fails to provide any reason why one of ordinary skill in the art would combine the elements in the same way as the claimed invention or reasons why one would disregard the teachings of Naughton to the use of one population of cells. As hindsight reconstruction is improper the Office Action has improperly rejected the Applicants' invention.

Therefore, combining Naughton with the other references does not reconstruct the claimed invention and claims 23, 25-26, 28, 33 and 36-37 are non-obvious and patentable. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection to claims 23, 25-26, 28, 33 and 36-37.

CONCLUSION

In view of the above remarks, Applicants' respectfully request reconsideration and allowance of the application. The Examiner is invited to call the undersigned at (617) 439-2948 if there are any questions.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 105447-0002.

Respectfully submitted,

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